UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CAMDEN VICINAGE

IN RE: VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION	MDL No. 2875 Honorable Robert R. Kugler, District Court Judge
This Document Relates to All Actions	Oral Argument Requested

DEFENDANTS' MEMORANDUM OF LAW IN OPPOSITION TO PLAINTIFFS' MOTION TO PRECLUDE OPINIONS OF DEFENSE EXPERT MICHAEL BOTTORFF, PHARM.D.

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page(s)

Cases

Other Authorities

Pursuant to Federal Rules of Evidence 104, 403, and 702, Defendants' Executive Committee, on behalf of all Defendants in this litigation, submit this memorandum of law in opposition to Plaintiffs' Motion to Preclude Opinions of Defense Expert Michael Bottorff, Pharm. D. (the "Motion") and state as follows:

INTRODUCTION

Plaintiffs seek to preclude Dr. Bottorff from offering two opinions: *one*, that NDMA and NDEA did not affect the bioequivalence of valsartan; *two*, that valsartan containing NDMA or NDEA has the same monetary value as valsartan free from NDMA or NDEA. *See* Motion at 1. Dr. Bottorff's opinions are admissible under Rule 702, and Plaintiffs' motion should be denied as to both opinions.

First, Dr. Bottorff's bioequivalence opinion is based not only on the bioequivalence studies that he evaluated of VCDs (which Plaintiffs focus on exclusively), but also on his analysis of the metabolic mechanisms of NDMA and NDEA compared to the metabolism of the active ingredients in valsartan (which applies the same across all manufacturers' valsartan). Dr. Bottorff discusses the pharmacokinetic processes of VCDs ***and*** nitrosamines extensively in his report, and he cites *multiple* sources to support his well-reasoned conclusion that NDMA and NDEA do not affect the bioequivalence of VCDs. Contrary to Plaintiffs' argument, his opinion is not based solely on the valsartan bioequivalence studies. Accordingly, Plaintiffs' criticisms—regarding the type of valsartan evaluated in the

bioequivalence studies Dr. Bottorff assessed and the range of bioequivalence studies Dr. Bottorff was provided—ring hollow. Numerosity of references is not a factor, and not surprisingly, Plaintiffs cannot point to any decision excluding an opinion based on the number of studies cited.[1] They have no bearing on Dr. Bottorff's ultimate conclusion in isolation and, in light of the totality of the data he considered, do *not* affect the reliability of his methodology.

Second, Plaintiffs have long been aware of Dr. Bottorff's opinion regarding the effect of nitrosamines on the monetary value of VCDs, which he offered in response to a question from Plaintiffs' counsel at his first deposition in September 2021. Moreover, Dr. Bottorff's opinion concerning the monetary value of valsartan is a logical extension of his opinion that NDMA and NDEA do not alter the bioequivalence of valsartan and that, therefore, the therapeutic response and efficacy of valsartan is unchanged.

For these reasons, as detailed below, Defendants respectfully submit that the Court should deny Plaintiffs' motion to preclude Dr. Bottorff's opinions.

LEGAL STANDARD

Rule 702 provides that "[a] witness who is qualified as an expert by knowledge, skill, experience, training, or education" may offer opinions in a case if

[1] Moreover, Plaintiffs ignore Dr. Bottorff's reliance list, which includes no fewer than 146 scientific studies. *See* Report of Michael Bottorff, Pharm. D., dated Jan. 12, 2022 ("Bottorff Class Cert. Rep."), Mot. Ex. B, Ex. B.

(i) the expert's "scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue"; (ii) "the testimony is based on sufficient facts or data"; (iii) "the testimony is the product of reliable principles and methods"; and (iv) "the expert has reliably applied the principles and methods to the facts of the case." Fed. R. Evid. 702. Applying the Supreme Court's guidance in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), the Third Circuit has explained that "[w]here a party objects to the admissibility to proffered expert opinion testimony, the court must examine '(1) the qualifications of the expert, (2) the reliability of the process or technique the expert used in formulating the opinion, and (3) the "fit" between the opinion and the facts in dispute.'" *R.D. v. Shohola, Inc.*, Case No. 3:16-cv-01056, 2019 U.S. Dist. LEXIS 198035, at *7 (M.D. Pa. Nov. 15, 2019) (quoting *Buzzerd v. Flagship Carwash of Port St. Lucie, Inc*., 669 F. Supp. 2d 514, 519 (M.D. Pa. 2009) (citing *In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717, 741-47 (3d Cir. 1994) ("*Paoli II*")).

In determining whether proposed testimony is sufficiently reliable, courts are to consider the following factors: (1) whether a method consists of a testable hypothesis; (2) whether the method has been subject to peer review; (3) the known or potential rate of error; (4) the existence and maintenance of standards controlling the technique's operation; (5) whether the method is generally accepted; (6) the relationship of the technique to methods which have been established to be reliable;

(7) the qualifications of the expert witness testifying based on the methodology; and (8) the non-judicial uses to which the method has been put. *Id.* (citing *In re Paoli R.R. Yard Pcb Litig.*, 35 F.3d 717, 742 n.8 (3d Cir. 1994)). "*Daubert* neither requires nor empowers trial courts to determine which of several competing scientific theories has the best provenance. It demands only that the proponent of the evidence show that the expert's conclusion has been arrived at in a scientifically sound and methodologically reliable fashion." *U.S. v. Mitchell*, 365 F.3d 215, 244 (3d Cir. 2004) (quoting *Ruiz-Troche v. Pepsi Cola Bottling Co*., 161 F.3d 77, 85 (1st Cir. 1998)). In other words, "any deficiencies in the evidence supporting [an expert's] conclusions and the correctness of those conclusions are relevant to the weight that his opinion should be given, not to its admissibility." *State Farm Fire & Cas. Co. v. Hartman Contrs.*, Case No. 14-cv-6535, 2017 U.S. Dist. LEXIS 75967, at *22 (E.D. Pa. May 17, 2017); *see also Broe v. Manns*, No. 15-985, 2016 WL 7048988, at *4 (M.D. Pa. Dec. 5, 2016) ("Any disagreement plaintiffs have with the expert can be dealt with through cross-examination, presentation of contrary evidence and proper jury instructions"); *In re Asbestos Prods. Liab. Litig*., 714 F. Supp. 2d 535, 544 (E.D. Pa. 2010) (noting defense experts' disagreement with plaintiff's expert's explanation for the lack of epidemiological studies supporting his opinion and concluding that "this does not negate the fact that [the expert's] opinions are based on generally accepted scientific methods and procedures, and that he gave a reasoned explanation

for his preferred methodology"); *In re Diet Drugs Prods. Liab. Litig.,* MDL No. 1203, 2000 WL 962545, at *13 (E.D. Pa. June 28, 2000) (finding that disagreement with the methods used by an expert is a question that "goes more to the weight of the evidence than to reliability for *Daubert* purposes").

ARGUMENT

I. DR. BOTTORFF'S OPINION THAT BECAUSE THERE IS NO OVERLAPPING METABOLIC PATHWAY BETWEEN NITROSAMINES AND VALSARTAN, THE PRESENCE OF NITROSAMINES IN VCDs COULD NOT AFFECT THE BIOEQUIVALENCE OF VALSARTAN IS FULLY SUPPORTED BY SCIENTIFIC AUTHORITY.

Plaintiffs' argument is misguided and side-steps the science supporting Dr. Bottorff's opinion. Dr. Bottorff acknowledges (rightfully) that various valsartan bioequivalence studies he considered did not evaluate valsartan containing nitrosamines. This is of no moment, as Dr. Bottorff explained several times in his deposition. As Dr. Bottorff testified, whether certain bioequivalence studies evaluated valsartan containing nitrosamines or valsartan without nitrosamines would have no bearing on his scientifically grounded conclusion that NDMA and NDEA have no effect on the bioequivalence of valsartan, because there is *no overlapping pharmacokinetic process*. *See* Transcript of Michael Bottorff, Pharm. D., dated March 25, 2022, (Mot. Ex. C) ("Bottorff March 2022 Dep.") 58:6-59:2. This is not *ipse dixit*. It is a logic, rooted in science. Dr. Bottorff's methodology meets the demands of Rule 702.

Dr. Bottorff provided a thorough report that assessed the bioequivalence of generic valsartan with the reference drug Diovan (*see* Bottorff Class Cert. Rep. 30), the bioequivalence of generic valsartan/amlodipine with the reference drug Exforge (*see id.* at 34), the bioequivalence of valsartan/HCTZ with the reference drug Diovan HCT (*see id.* at 37), and the bioequivalence of generic valsartan/amlodipine/HCTZ with the reference drug Exforge HCT (*see id.* at 39). Importantly, Dr. Bottorff assessed the pharmacokinetics of VCDs *and* the mechanisms for metabolism of NDMA and NDEA. (*See id.* at 22-24, 47-50.) These analyses allowed Dr. Bottorff to scientifically conclude that neither NDMA nor NDEA alter the bioequivalence of valsartan.

As Dr. Bottorff explained in great detail, nitrosamines and valsartan do not have a common pathway of metabolism.

> After oral administration in humans, valsartan is absorbed into the body primarily in the small intestine (below the level of the stomach) and reaches peak plasma concentrations between two and four hours. The amount of a given dose that reaches the systemic circulation (beyond the liver) is expressed by the term absolute bioavailability, and this ranges from 10-35%, averaging 25%. This means that only ¼ of a valsartan dose, on average, actually circulates in the blood stream to reach the AT1 receptor sites, the valsartan mechanism of action. After absorption in the body, the first organ to see valsartan, the liver, uses CYP2C9 to metabolize only a very small amount, about 11%, producing an inactive metabolite. Because of such a small amount of reliance on the CYP2C9 pathway, the potential for P450 based drug interactions is negligible. About 80% of valsartan is excreted unchanged and found in the feces. Most of this fecal elimination comes from biliary excretion from the liver. Thus, there is very little actual metabolism of valsartan, and no significant drug interactions involving

> valsartan ADME have been identified. . . . ***With this pharmacokinetic and pharmacodynamics profile, nitrosamines like NDMA/NDEA would not alter the pharmacokinetics of or response to valsartan since there is no common pathway of metabolism or alteration of its metabolism or effect***.

(*Id.* at 22-23 (emphasis added) (footnotes omitted).).[2] Dr. Bottorff later details the metabolism process for NDMA and NDEA, thus demonstrating the complete lack of overlap in the above-described pharmacokinetic processes of valsartan compared to the body's metabolism of NDMA and NDEA.

> [O]rally administered NDMA and NDEA, such as the NDMA/NDEA present in valsartan, are absorbed through the upper small intestine with a half-life of absorption of three minutes and then directly circulated to the liver for metabolism. The absorption process is described as first-order, meaning that absorption is not saturable. Although many CYP enzymes are found in the gut wall and are able to metabolize a compound prior to reaching the liver, neither CYP2E1 nor CYP2A6 is found in the gut wall; thus CYP-mediated metabolism of NDMA and NDEA following oral administration would be isolated to the liver, until a dose was given that exceeded the first-pass capacity of the liver. . . . Oral doses at the levels detected in the generic valsartan at issue in this litigation are metabolized in the liver almost completely, preventing exposure to other tissues and organs.

(*Id.* at 47-48 (footnotes omitted).)[3] The various excerpts Plaintiffs cite establish only that various bioequivalence studies may not have been conducted using valsartan containing NDMA or NDEA. But that misses the point, as Dr. Bottorff pointed out

[2] Dr. Bottorff cited numerous studies in this section of his report. (*See* Bottorff Class Cert. Rep. nn. 12-16.)

[3] Again, Dr. Bottorff cited numerous studies in this section of his report. (*See* Bottorff Class Cert. Rep. nn. 33-38.)

repeatedly during his deposition.

> Q: And if Torrent's valsartan was not contaminated with nitrosamines back in 2010, these bioequivalenc[e] studies don't tell you anything in relation to if nitrosamines impact the bioequivalence of valsartan, correct?
>
> A: And, again, as I said before, not in and of themselves. But as we keep working through this, you'll see one of the premises about having combination products with more than valsartan, like hydrochlorothiazide in six-and-a-half – or six-and-a-quarter up to 25 milligrams, amlodipine 5 or 10 milligrams, having no effect on the bioequivalence of – of valsartan ***because of the lack of overlapping metabolic pathways***.
>
> And so as I've – I've demonstrated in both reports, *the lack of an overlapping metabolic pathway between the nitrosamines and valsartan, that there would be no reason, and in fact* ***there couldn't be any reason, to have that have any effect on the bioequivalence of valsartan***.

(Bottorff March 2022 Dep. 58:6-59:2 (emphasis added).)

> Q: And you think that studies done without nitrosamines can tell you if nitrosamines are going to impact the bioequivalenc[e]?
>
> . . .
>
> A: Again, I think in answering that previously, I said that not in and of themselves. You have to look at the whole picture. And part of the whole picture is valsartan's bioequivalence is retained in the presence of other compounds, that I had to see the data for, before I could draw that conclusion.
>
> . . .
>
> Q: You just testified that you have to look at the whole picture. What do you mean by the whole picture?
>
> A: *Look at all the compounds involved, their metabolic pathways, the*

bioequivalence studies.

(*Id.* at 68:196-69:18 (emphasis added).)

In light of the full scope of Dr. Bottorff's analysis—not solely his analysis of the bioequivalence studies for VCDs *but also* his analysis of the metabolic pathways of VCDs and nitrosamines—Plaintiffs' criticism of the bioequivalence studies do not render Dr. Bottorff's opinion unsupported or unreliable. Similarly, Plaintiffs' criticism of the range of studies Dr. Bottorff was provided also does not render Dr. Bottorff's opinion unsupported. He relied on numerous scientific sources. *See, e.g.*, Bottorff Class Cert Rep., Ex. B. Dr. Bottorff employed a reliable methodology, and his conclusion regarding NDMA and NDEA's effect on the bioequivalence of valsartan is a logical conclusion flowing from the facts he considered. "A court must examine the expert's conclusions to determine *whether they could reliably follow from the facts known to the expert and the methodology used*." *Pease v. Lycoming Engines*, Case No. 4:10-cv-843, 2011 U.S. Dist. LEXIS 145344, at *28 (M.D. Pa. Dec. 19, 2011) (quoting *Heller v. Shaw Indus., Inc.*, 167 F.3d 146, 153 (3d Cir. 1999) (emphasis added)). "[A]s long as an expert's scientific testimony rests upon 'good grounds', based on what is known, it should be tested by the adversary process—competing expert testimony and active cross-examination—rather than excluded from jurors' scrutiny for fear that they will not grasp its complexities or satisfactorily weigh its inadequacies." *Terry v. McNeil-PPC, Inc. (In re Tylenol (Acetaminophen)*

Mktg., Sales Practices, & Prods. Liab. Litig.), MDL No. 2:13-md-2436, 2016 U.S. Dist. LEXIS 97368, at *5 (E.D. Pa. July 26, 2016).

If Plaintiffs believe that the only evidence that could lead an expert to conclude that nitrosamines have no effect on the bioequivalence of valsartan must come from bioequivalence studies evaluating valsartan containing nitrosamines, Plaintiffs are free to try and make this argument to the jury or through the cross-examination of Dr. Bottorff. Notably, Plaintiffs' Motion does not cite to any expert report or testimony for this proposition. *See generally* Motion. This is because despite having a plethora of experts address bioequivalence across multiple phases of expert discovery, none has stated the position Plaintiffs now advance because the argument simply is not scientifically supportable. Regardless, the fact that Plaintiffs may try and introduce a different purported methodology does not render Dr. Bottorff's methodology unreliable. "*Daubert* does not set up a test of which opinion has the best foundation, but rather whether any particular opinion is based on valid reasoning and reliable methodology. . . . If disagreements on particular points between proposed experts and others in their field were a proper basis for questioning the reliability and relevance of the methods employed by the experts, it is likely that very few expert opinions would be admissible at trial." *In re Asbestos Prods. Liab. Litig.*, 714 F. Supp. 2d at 546-47 (quoting *Johnson v. Van Line Bunkering*, Case No. 1-cv-5819, 2003 U.S. Dist. LEXIS 23698, at *6 (E.D. Pa. Dec.

30, 2003)). Dr. Bottorff's opinion meets the requirements of Rule 702. Accordingly, Plaintiffs' motion should be denied.

II. THERE IS NO BASIS TO EXCLUDE DR. BOTTORFF'S OPINION CONCERNING THE LACK OF ANY DIFFERENCE ON THE MONETARY VALUE OF THE VCDs AT ISSUE.

Plaintiffs seek a ruling from the Court "confirm[ing] . . . that Dr. Bottorff will not be offering any opinions relative to the monetary value of contaminated VCDs in this action." *See* Motion at 17. Plaintiffs are not entitled to the relief they seek.

While Plaintiffs assert that Dr. Bottorff did not sufficiently disclose opinions about the monetary value of VCDs, they admit that these opinions were raised in Dr. Bottorff's first "deposition on ***September 16, 2021***." *See* Motion at 17 (emphasis added). Defendants note that they have not designated Dr. Bottorff to address issues related to the monetary value of VCDs, and Dr. Bottorff has testified that he does not plan to discuss monetary value. (*See* Transcript of Deposition of Michael B. Bottorff, dated Sept. 16, 2021 ("Bottorff 2021 Dep.") (Mot. Ex. D) 17:10-11. Instead, Dr. Bottorff's opinion focuses on the *therapeutic value* of the valsartan at issue. As Dr. Bottorff explained in his report:

> The presence of NDMA/NDEA in valsartan could not have had any effect on the pharmacokinetics, pharmacodynamics, bioavailability or bioequivalence of valsartan generic products. The compounds do not share any known pharmacokinetic or pharmacodynamic mechanism The presence of active, intended ingredients with valsartan, such as HCTZ and/or amlodipine, also did not alter valsartan bioequivalence for the same reason(s), that is no overlapping pharmacokinetic process. ***Thus, there is no conceivable way for NDMA/NDEA, merely by being***

> ***present, to alter the bioequivalence of valsartan, and thus its therapeutic response and efficacy***.

(*See* Bottorff Class Cert. Rep. at 52 (emphasis added).) The issue of the "monetary value" of VCDs, however, was specifically raised by *Plaintiffs'* counsel during Dr. Bottorff's September 16, 2021 deposition:

> Q: Okay. So I want to explore just some of your opinions first and the basis for those opinions. And so, kind of reading through here, I guess my first question is, Dr. Bottorff, ***is it your opinion that generic valsartan contaminated with NDMA or NDEA has the same monetary value as generic valsartan without NDMA or NDEA***?
>
> . . .
>
> A: So the question, as I understand it, is the same monetary value?
>
> Q: Correct.
>
> A: I believe it would be.
>
> Q: And what's the basis for your opinion on that?
>
> A: Because ***I don't see how it substantially changed the effectiveness of the drug***.

(Bottorff 2021 Dep. 14:3-24 (emphasis added). This opinion is an appropriate and logical extension of Dr. Bottorff's bioequivalence opinion. Because Dr. Bottorff opines that nitrosamines have no effect on the bioequivalence of valsartan, its therapeutic effect, or efficacy, it follows that there would be no difference in the monetary value of valsartan containing nitrosamines and valsartan not containing nitrosamines. *See, e.g.*, *Diawara v. United States*, Case No. 18-cv-3520, 2020 U.S.

Dist. LEXIS 197070, at *14-15 (E.D. Pa. Oct. 2223, 2020) (citing *United States v. Barrett*, 117 F. App'x 216, 219 (3d Cir. 2004) (district court properly admitted expert testimony that was a "logical and reasonable inference from the language contained in the [expert's] report").

Further, any objections to Dr. Bottorff's opinions on the issue of monetary value should have been raised long ago. Case Management Order 23 required Rule 702 motions regarding general causation experts to be filed by November 1, 2021. *See* CMO 23 [Doc. 863]. Plaintiffs motion to exclude Dr. Bottorff at the general causation phase was filed on November 1, 2021, and did not raise *any* concern about Dr. Bottoff's testimony regarding the monetary value of VCDs. *See* Plaintiffs' Nov. 1, 2021 Motion to Preclude Dr. Bottorff [Doc. 1712]. Notably, the Court denied that motion in its entirety. *See* Daubert Order No. 2 [Doc. 1974] at 3 ("[T]he methodology that grounds Dr. Bottorff's opinion is acceptable in the relevant scientific community."). In addition, following the submission of Dr. Bottorff's January 12, 2022 class certification report, Plaintiffs again failed to raise any issue with his general causation testimony regarding monetary value. *See* Plaintiffs May 3, 2022 Motion to Strike [Doc. 2043]. As a result, Plaintiffs cannot claim that they have been unfairly surprised by such opinions.

Dr. Bottorff's opinion concerning the monetary value of the VCDs at issue is fully consistent with the opinions offered in his 2022 report concerning the effect of

NDMA and NDEA on the efficacy of valsartan—and Plaintiffs have had the opportunity to explore such opinions, and the bases for them, at Dr. Bottorff's depositions. Accordingly, Plaintiff's belated effort to exclude these opinions should be rejected.

CONCLUSION

For the foregoing reasons, Defendants respectfully request that the Court deny Plaintiffs' Motion to Preclude Opinions of Michael Bottorff, Pharm. D.

Dated: April 11, 2023

Respectfully Submitted:

By: */s/ Victoria Davis Lockard*

GREENBERG TRAURIG, LLP
Lori G. Cohen
Victoria Davis Lockard
Steven M. Harkins
Terminus 200
3333 Piedmont Road, N.E.,
Suite 2500
Atlanta, Georgia 30305
Tel. (678) 553-2100
Fax. (678) 553-2386
CohenL@gtlaw.com
LockardV@gtlaw.com
HarkinsS@gtlaw.com

Counsel for Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries Ltd., Actavis Pharma, Inc., and Actavis LLC

Jessica Davidson (DC Bar No. 457021)
(Admitted to Practice in Maryland and the District of Columbia; Not Admitted in New York)
Liaison Counsel for Manufacturer Defendants
Allison M. Brown
SKADDEN, ARPS, SLATE, MEAGHER & FLOM LLP
One Manhattan West
New York, NY 10001 20005
Tel.: (212) 735-2588
Fax: (212) 777-2588
jessica.davidson@skadden.com
Allison.brown@skadden.com

SKADDEN, ARPS, SLATE, MEAGHER & FLOM LLP
Nina R. Rose
1440 New York Ave., N.W.
Washington, D.C. 20005
Tel.: (202) 371-7000
Fax: (202) 661-0525
nina.rose@skadden.com

Counsel for Zhejiang Huahai Pharmaceutical Co, Ltd., Huahai U.S., Inc., Prinston Pharmaceutical Inc. and Solco Healthcare U.S., LLC

KIRKLAND & ELLIS LLP
Devora W. Allon
Alexia R. Brancato
601 Lexington Avenue
New York, New York 10022
Tel: (212) 446-5967
Fax: (212) 446-6460
Devora.allon@kirkland.com
Alexia.brancato@kirkland.com

Attorneys for Torrent Pharmaceuticals Ltd. and Torrent Pharma Inc.

CERTIFICATE OF SERVICE

I hereby certify that on April 11, 2023, I caused a copy of the foregoing document to be served on all counsel of record via CM/ECF.

/s/ Steven M. Harkins
Steven M. Harkins
Greenberg Traurig, LLP